DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 16-192/S-043
NDA 16-776/S-036

JAN 2 6 1999

Zeneca Pharmaceuticals
Attention: Mr. Robert J. Orzolek
1800 Concord Pike
P.O. Box 15437
Wilmington, DE 19850-5437

Dear Mr. Orzolek:

Please refer to your supplemental new drug applications dated November 20, 1998, received November 23, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sorbitrate (isosorbide dinitrate) Oral (NDA 16-192) and Chewable Tablets (NDA 16-776).

This supplemental new drug application provides for final printed labeling revised by adding the following in bold print as the first paragraph of the **WARNINGS** section of the labeling:

> **Amplification of the vasodilatory effects of Sorbitrate by sildenafil can result in severe hypotension. The time course and dose dependence of this interaction has not been studied. Appropriate supportive care has not been studied, but it seems reasonable to treat this as a nitrate overdose, with elevation of the extremities and with central volume expansion.**

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the final printed labeling included in your November 20, 1998 submission. Accordingly, these supplemental applications are approved effective on the date of this letter.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Mr. Gary Buehler
Regulatory Health Project Manager
(301) 594-5332

Sincerely yours,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research